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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,814	08/29/2003	Gretchen M. Unger	GSL01/C	2748

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EXAMINER	
POPA, ILEANA	
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1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,814	UNGER, GRETCHEN M.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,67,87-94 and 133-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 66-95,97-100,102-109,111-116,118,119,122-124,126,127 and 133-141.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 68-86,95,97-100,102-109,111-116,118,119,122-124,126 and 127.

DETAILED ACTION

1. Claims 1-65, 96, 101, 110, 117, 120, 121, 125, and 128-132 have been cancelled. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 have been withdrawn. Claim 66 has been amended.

Claims 66, 67, 87-94, and 133-141 are under examination.

Information Disclosure Statement

2. The IDS forms of 08/12/2008, 07/25/2008, 06/27/2008, 06/19/2008, and 06/11/2008 have been considered. It is noted that the foreign documents DE 4341114, DE 4411557, and DE 19723308 listed in the IDS form of 06/27/2008 have been lined through because Applicant did not provide an English translation of the document, nor did Applicant provide an English abstract.

Specification

3. The use of the trademarks Qiaquik, Zymoclean, Synergel, SybrGold, and Storm 860 has been noted in this application (p. 23, lines 20-25). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Response to Arguments

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25-28 of copending Application No. 11/622,359 because Applicant did not submit a terminal disclaimer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and

a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136.

The application claims drawn a collection of particles having a bioactive component, a surfactant with an HLB less than 6.0, a biocompatible polymer, and a cell recognition component having affinity for a cell receptor; the average diameter of the particles is less than 50 nm as measured by atomic force microscopy after drying of the particles (claim 25), wherein the bioactive component is a polynucleic acid (claim 28) and wherein the biocompatible polymer is tenascin claims 26 and 27). The specification defines that: **(i)** the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (i.e., a surfactant that has an HLB of less than 5.0, as recited in the instant claims 87, 88, 90, and 136), **(ii)** the particles comprise surfactant micelles containing surfactant and a bioactive agent, **(iii)** the biocompatible polymer forms a shell surrounding the surfactant micelles, and **(iv)** the biocompatible polymer is precipitated by cations such as Li^+ (p. 9. lines 21-23. p. 10, lines 1-21, p. 75, lines 15-18, p. 76, lines

3-13). With respect to the limitation of nanocapsule, the specification disclosed that the particles can be formulated as nanocapsules (p. 11, lines 6 and 7). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing agents are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims and the instant claims are obvious variants of one another.

6. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671 because Applicant did not submit a terminal disclaimer.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid

condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88), the surfactant can be non-ionic (claim 87) or is selected from the group recited in claims 90 and 136, the composition further comprises a water-miscible solvent (claim 93).

The patent claims recite a plurality of particles comprising a surfactant with an HLB less than 5.0, a bioactive hydrophobic component (i.e., a bioactive component), and a biocompatible polymer, wherein the particles have an average diameter of less than 50 nm as determined by atomic force microscopy and wherein the biocompatible polymer is precipitated in the presence of a cation (claims 29, 37, and 42). The surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (claim 33), as recited in the instant claims 87, 90, and 136, and the particles further comprise a water-miscible solvent (claim 31). With respect to the limitation of the biocompatible polymer providing specific cellular uptake, the specification discloses that the biocompatible polymer can be tenascin (see fig. 7B, and also column 3, lines 6-8). The specification discloses that the biocompatible polymer forms a shell surrounding the surfactant micelles containing the bioactive component and the surfactant, the hydrophobic bioactive component can be a polynucleic acid, and that the precipitating cation is Li^+ (Abstract, column 3, lines 25-32, column 5, lines 37-59, column 7, lines 32-37, column 9, lines 40-45, column 10, lines 42-66, column 15, lines 30-32). With respect to the limitation of HLB being less than 6.0, the patent claims recite an HLB less than 5.0 that anticipates the claimed HLB of less than 6.0. With respect to the limitation of nanocapsules, the specification discloses that the particles are formulated as nanocapsules (Abstract). With respect to the limitation of the polynucleotide being

associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Therefore, the patent claims and the instant claims are obvious variants of one another.

7. The provisional rejection of claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999 is withdrawn because Application No. 10/958,999 has been abandoned. However, new grounds of rejections are made below over claims 8 and 11 of Application No. 12/027,863, which is a continuation of Application No. 10/958,999. It is noted that claims 8 and 11 of Application No. 12/027,863 are identical to claims 10 and 13 of the abandoned Application No. 10/958,999.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 66, 67, 87, 88, 90-94, 135, and 137-139 remain rejected under 35 U.S.C. 102(e) as being anticipated by Unger et al. (US Patent No. 6,139,819), as evidenced by Kondo et al. (Anal Chem, 1991, 198: 30-35, Abstract).

Unger et al. teach particles comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139) (column 6, lines 52-61, column 8, lines 1-3 and 44-47, column 14, lines 10-12, column 15, lines 62-65, column 16, lines 18-26, column 17, line 60, column 18, line 61, column 30, lines 18-32 , 66, and 67, column 31, lines 29 and 30, column 34, lines 24-49, column 38, lines 13-17, column 48, lines 43-45, column 49, lines 1-8, column 59, lines 66 and 67, column 60, lines 1-4 and 16-24). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137) (column 9, lines 36-50, column 10, lines 13-23, column 60, lines 16-21). Unger et al. teach their particles as having a hollow core comprising the bioactive agent (column 60, lines 1-4 and 16-24), i.e. they teach nanocapsules (see also Applicant's definition of nanocapsules, on p. 5, lines 21-24 of the instant specification). Unger et al. also teach that the particles have a size of about 30 nm (claims 66 and 139) (column 28, lines 51-

53), that the particles can comprise a combination of two or more surfactants (claim 91) (column 19, lines 21-25, column 31, lines 52-57), a biocompatible oil, such as peanut oil (claim 92) (column 33, lines 23-25), and a water-miscible solvent (claim 93) (Example 4). With respect to the limitation of the protein shell being precipitated by the cation, wherein the cation is Li^+ (claims 66 and 139), this is inherent to the nanocapsules of Unger et al., since the covalent attachment of the targeting ligand requires addition of lithium aluminum hydride (see above), which would necessarily result in a precipitated protein shell (it is noted that Li^+ is known in the art as a protein precipitating agent, see for example Kondo et al., Abstract). Since Unger et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

Applicant traversed the instant rejection on the grounds that the first test of anticipation is to determine if the reference discloses a specific embodiment which satisfies all the limitations of the claimed invention; the reference embodiment must be in the full detail and presented order of the claimed invention. Applicant argues that Unger et al. does not disclose such an embodiment, i.e., a surfactant micelle comprising a therapeutic bioactive component and a hydrophobic surfactant, surrounded by a precipitate shell comprised of a polypeptide and a cationic precipitating agent, which provides cell-targeted delivery and uptake via receptor mediation, in a capsule measuring less than about 50 nm in diameter (claim 66). Claim 138 repeats these limitations, and adds the limitation that the cationic precipitating agent is Li^+. Applicant submits that the smallest particle disclosed by Unger et al. in Example 39A is a simple, 200 nm albumin-glutaraldehyde mixture; this prophetic example discloses

neither a hydrophobic surfactant nor a precipitate shell comprising a polypeptide and cationic precipitating agent. Therefore, Applicant argues, a specific embodiment of the present invention is not taught by Unger et al.

In addition Applicant argues that, if a reference does not disclose a specific embodiment of the claimed invention, a second test of anticipation is available, i.e., to determine if Unger et al. direct the ordinary artisan to the instant claimed invention, assessing whether the totality of Unger et al. "provides a 'pattern of preferences' which describes the claimed invention without the necessity for judicious selection from various disclosures thereof; if the determination is negative, anticipation is not established. Applicant submits that one of skill in the art would not envisage the instant claimed invention in view of the pattern of preferences disclosed by Unger et al. The following discussion relates to Unger et al's pattern of preferences. Applicant submits Unger et al as a whole teaches 200 nm to micron-sized formulations of inert gas or gaseous precursors encapsulated in flexible lipids for use in conjunction with ultrasound for the visualization or rupture of said formulation at a targeted extracellular site (column 3, lines 66-67, column 4, lines 1-2 and 6-41, column 5, lines 56-58). Applicant also submits that the pattern of preferences in Unger et al. contrasts markedly with Applicant's claims 66 and 138 (column 7, lines 28-59; column 8, lines 42-43; column 17, lines 44-49; column 23, lines 38-45; column 26, lines 31 and 32; column 27, lines 44-52; column 28, line 57; column 29, lines 56-58; column 30; lines 59-62; column 34, lines 53-55; column 36, lines 64-67; column 37, lines 25-29; column 41, lines 66 and 67; column 53, lines 42-51; column 54, lines 32-44; column 55, lines 1-5; column 81; lines 64-67;

column 82, lines 1 and 2). Applicant argues that the Examiner's finding of anticipation necessarily requires that one of skill in the art would be directed by Unger et al.'s preferred-pattern of disclosures and examples, in clear and unequivocal terms, to envision, for example, the use of: a therapeutic bioactive agent of the claimed invention vs. the reference's preferred inert gas; a surfactant micelle comprising a therapeutic bioactive agent and a hydrophobic surfactant (lipid) vs. the Unger et al.'s preferred vesicle comprising a lipid (hydrophobic or hydrophilic - the reference states no preference) with a void that is filled with inert gas or gaseous precursors; a precipitate shell comprising a polypeptide and a cation lithium, vs. Unger et al.'s preferred lipid (with no mention of a precipitating cation lithium) that will impart size-altering flexibility to the vesicle; and receptor-based uptake vs. Unger et al.'s preference of using ultrasound to rupture vesicle outside the cells; and doing all of this so as to achieve the precise combination of the claimed invention.

Further, Applicant submits that Unger et al. provide no clear and unequivocal direction such that an artisan of ordinary skill could make a "vesicle" with a size of 30 nanometers (column 28, line 52) and in all other aspects identical to the instantly claimed composition, particularly in view of Unger et al.'s teaching that the most preferred "vesicle" size is 200 nm to about 7 μm and in view of Unger et al. defining "vesicle" as "liposomes, micelles, bubbles, microbubbles, microspheres, lipid-, polymer-protein- and/or surfactant-coated bubbles, microbubbles and/or microspheres, microballoons, aerogels, clathrate bound vesicles, and the like", and teaching that all of which may or may not include a bioactive agent, and all of which may not include a

targeting ligand. Applicant argues that, because this definition is so broad, it would be impossible for one of ordinary skill in the art to envisage what specific "vesicle" embodiment is being disclosed with respect to this minimum size. Applicant argues that one of skill in the art might then look to Unger et al.'s Examples for further information, and upon doing so, one of skill in the art would be guided even further away from the compositions of the instant claims. In view of the above, Applicant submits it is improbable that one of ordinary skill in the art would envision the instant invention upon the reading of Unger et al. Applicant submits that the Examiner's choosing of several elements from the vast disclosure of Unger et al. is not sufficient to establish anticipation to the exclusion of considering whether one of ordinary skill in the art would envisage the instant claimed invention in complete and exact terms upon reading Unger et al. With respect to size, Applicant points out that the passage indicated by the Examiner (i.e., column 28, lines 60-62) disclose 30 μm and 12 μm vesicles, not 30 nm and 12 nm vesicles, as asserted by the Examiner. Applicant submits that any generic disclosure of small sizes in Unger et al. does not support an anticipation of the claimed invention, based upon requirements for the reference to provide clear and unequivocal direction to the invention. Applicant argues that MPEP § 2131.03 (II) states that "[w]hen the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation." The disclosed size range of Unger's vesicles is between 30 nanometers and about 100 micrometers, allegedly overlapping Applicant's claimed size of less than about 50 nanometers. However, none of the

Examples in Unger et al. disclose a vesicle of less than about 200 nanometers. Accordingly, the instant situation falls squarely within the scope of this section of the MPEP, necessitating that the Examiner undertake a determination as to anticipation specific to this particular case. The MPEP then continues (at § 2131.03(II)), "If the claims are directed to a narrow range, and the reference teaches a broad range ....it may be reasonable to conclude that the narrow range is not disclosed with 'specific specificity' to constitute an anticipation of the claim," citing Atofina v. Great Lakes Chem. Corp., 441 F.3d 991,999 (Fed. Cir. 2006). In Atofina, Applicant argues, the court held that the disclosure in the prior art was only that of a range, not a specific temperature in that range, and "the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." Atofina, 441 F.3d. Applicant's claimed size is a specific species of all possible size ranges of particles. Importantly, the size species claimed by Applicant is the size cutoff for efficient caveolae uptake of Applicant's particles into cells, allowing for avoidance of destruction of the particles by lysosomes within the cells (e.g., see Example 2 of the instant specification). In contrast, Unger et al. provides no similar description of his stated 30 nm threshold. In view of the above, it is evident the size of 30 nm is in fact only a generic disclosure of Unger et al., and therefore, Unger et al. does not disclose the claimed range and does not serve as an anticipation of Applicant's claims.

With respect to the Examiner's assertion that the covalent attachment of the targeting ligand using LAH would inherently result in a precipitate shell comprising protein and lithium, Applicant argues that such an assertion is misplaced and

contradictory to accepted scientific principles. Applicant points out that the instant application teaches a precipitate shell formed by using aqueous ions (including, for example, lithium) to displace solute bonding to water (i.e., a phenomenon known as "salting out"); one skilled in the art would understand the resulting precipitate shell would be comprised of for example a polypeptide and ions (including for example lithium). In contrast, Applicant argues, Unger et al teach the use of the reducing agent lithium aluminum hydride (LAH) to render more permanent, Schiff-base linkages for covalently coupling ligands. Applicant argues that the reference (taken with Kondo) is not equivalent to the claimed lithium precipitate, for several reasons. First, it is well known in the art that LAH is a highly reactive and nonselective reducing agent such that a conventional practice is to expose the final product (for example the desired ligand conjugate) to LAH for only 30 minutes, in order to degrade it for thin layer chromatography analysis (Thompson & Lee (1965) BBA 55068:151-9; Wood & Snyder (1967) Lipids 3(20:129-35). LAH reacts explosively with water, and thus conjugations using LAH are executed in water-insoluble ether, followed by careful drop wise addition of water to decompose the LAH into its subcomponents (lithium ion, aluminum ion and hydrogen gas), followed by separation of the desired final conjugation product away from the water-soluble lithium by multiple extractions with ether (Nystrom & Brown (1947) JACS 69:2548-9; Smith & Ho (1972) JOC 37(4):653-6). Therefore, to avoid degradation of the product conjugate, one skilled in the art would purify the desired product conjugate (e.g., ligand) from lithium. Second, it is well established that LAH-mediated reduction reactions are effected by transferring the negative hydride anion,

and not the positive lithium cation, to the product (Nystrom & Brown (1947) JACS 69:2548-9; Smith & Ho (1972) JOC 37(4):653-6). Thus lithium is a reaction side product, not a part of the final product. Third, with respect to Kondo et al., the authors describe the use of lithium chloride in a process to purify DNA plasmid away from cellular RNA and protein. The claimed invention does not teach the use of lithium to remove RNA and protein from DNA. Rather, the claimed invention teaches the use of lithium to stabilize nanocapsules comprising for example DNA cargo and a protein shell. Examiner has not properly supported the assertion that a shell comprising a lithium precipitate is inherent in Unger et al., by articulating a rationale grounded by appropriate scientific principle.

With respect to Examiner's assertion that Unger et al teaches their "nanocapsules" as being suitable for the intracellular delivery of DNA, as evidenced by Example 42 (non-final Office action of Non-Final Rejection, page 15), Applicant submits the particle in the cited example is a simple cationic liposome of undefined size, and not the composition of the claimed invention. Moreover, there is no disclosure in this example or in the reference as a whole that would direct one skilled in the art from this cationic liposome to the claimed invention.

Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

It is noted that most of the Applicant's arguments are based on recent decisions by the Board of Patent Appeals and Interference (filed as 132 Declarations on

07/30/2008 and 06/11/2008). With respect to this issue, the Examiner would like to point out that this is a different application under a different examination, and therefore, the decisions by the Board of Patent Appeals and Interference regarding other applications and examinations are not binding.

Applicant argues that, to be anticipatory, a reference (i) must disclose a specific embodiment which satisfies all the limitations of the claimed invention; this embodiment must be in the full detail and presented in the order of the claimed invention, and (ii) the pattern of preferences disclosed in the reference must direct the ordinary artisan to the instant claimed invention. In response to this argument, it is noted that there is nothing in MPEP supporting such. The following is a citation from MPEP:

> 2123 [R-5] Rejection Over Prior Art's Broad Disclosure Instead of Preferred Embodiments
>
> I. PATENTS ARE RELEVANT AS PRIOR ART FOR ALL THEY CONTAIN
>
> The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).
>
> A reference may be relied upon for all that it would have reasonably suggested to onehaving ordinary skill the art, including nonpreferred embodiments. Merck & Co. v.Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Upsher-Smith Labs. v. Pamlab, LLC, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005) (reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

II. NONPREFERRED AND ALTERNATIVE EMBODIMENTS CONSTITUTE PRIOR ART

> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The invention was directed to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability" and "some degree of flexibility," but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art." 27 F.3d at 554, 31 USPQ2d at 1132.). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Therefore, MPEP clearly states that **(i)** a reference which clearly names the claimed species anticipates the claimed invention no matter how many species are named, **(ii)** nonpreferred and alternative embodiments constitute prior art, and **(iii)** disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments.

With respect to Atofina, the court held that a reference temperature range of 100-500°C did not describe the claimed range of 330-450°C with sufficient specificity to be anticipatory; further while there was a slight overlap between the reference's preferred range (150-350°C) and the claimed range, that overlap was not sufficient for anticipation. It is noted that in Atofina, the reference did not specifically recite a species

with the claimed range, i.e., the reference did not positively recite a temperature of 330 or 450°C, nor did the reference positively recite a temperature within the claimed 330-450°C range. The instant case is different because the reference positively recites 30 nm, i.e., a species within the claimed range of "less that 50 nm"; such a recitation of a species within the claimed range was absent in Atofina. Because they positively disclose the species of 30 nm, which is less that 50 nm, Unger et al. anticipate the claimed range of "less than 50 nm".

It is noted that Applicant also argues that the instant particles, due to their small size and stabilization with a precipitated protein shell are able to deliver their cargo intact into the cells and also are able to avoid lysosomal degradation; the size species claimed by Applicant is the size cutoff for efficient caveolae uptake of Applicant's particles into cells, allowing for avoidance of destruction of the particles by lysosomes within the cells (e.g., see Example 2 of the instant specification). In contrast, Unger et al. provides no similar description of his stated 30 nm threshold. In response to this argument, it is noted that such a limitation (i.e., avoiding lysosomal degradation) is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). And even if such a limitation would be recited in the claims, the rejected claims are drawn to a composition and not to a method of delivery which avoids lysosomal degradation; reciting such would be an intended use which would not state any distinct definition of any of the claimed limitations such as to differentiate the claimed composition from the

composition taught by the prior art and therefore, would not impart patentability to composition claims.

With respect to a precipitated shell, Unger et al. teach such. Unger et al. teach using lithium aluminum hydride (LAH) to couple their targeting ligands to the protein shell. While Applicant is right in stating that LAH is explosive in water, as Applicant points out that conjugation using LAH is done in ether, followed by careful drop-wise addition of water to decompose the LAH into its subcomponents (lithium ion, i.e., Li^+, aluminum ion and hydrogen gas). By doing this, protein shell is necessarily exposed to aqueous Li^+, which exposure would necessarily result in a precipitated protein shell comprising Li^+; this is because Li^+ is a protein precipitating agent (see Kondo et al.). Applicant does nothing different from what Unger et al. do, i.e., both Applicant and Unger et al. expose their particles to Li^+. Subsequent washings would not remove protein shell-associated Li^+. The arguments that Unger et al. use LAH for a different purpose or that LAH is a nonselective reducing agent are irrelevant, because the outcome is still a precipitated shell. The argument that, since LAH-mediated reactions take place by transferring the negative hydride anion and not the positive lithium ion, lithium is not a part of the final product is not found persuasive. While it might be true that the negative hydride anion is part of the final product, the protein shell is exposed to aqueous Li^+; as noted above, such exposure would necessarily result in precipitating the shell and the retention of Li^+ the precipitated shell. The argument that LAH is used for only 30 minutes, in order to degrade the desired conjugate for thin layer chromatography analysis is misplaced. The papers cited by Applicant (i.e., Thompson

& Lee, BBA, 1965, 55068:151-9; Wood & Snyder, Lipids, 1967, 20:129-35) are concerned with totally different reactions, i.e., they are concerned with cleaving carboxylate and phosphate esters of neutral lipids and not Schiff base linkages; therefore, their teachings have nothing to do with reducing the instable Schiff base linkages by LAH to form the stable, covalent linkages between the protein shell and the targeting ligand of Unger et al. (see column 49, lines 1-6); clearly, LAH does not degrade the desired conjugate of Unger et al. With respect to Kondo et al., Applicant points out that they describe the use of lithium chloride in a process to purify DNA plasmid away from cellular RNA and protein. Applicant argues the claimed invention does not teach the use of lithium to remove RNA and protein from DNA. Such an argument is irrelevant because Kondo et al. was only cited to evidence that the presence of Li^+ induces protein precipitation. The fact of the matter is that Li^+ does precipitate proteins and therefore, Unger et al. anticipate the limitation of a precipitated protein shell comprising Li^+. Therefore, the Examiner's assertion that a precipitating shell comprising Li^+ is inherent to the composition of Unger et al. is not misplaced and it is in accordance with the accepted scientific principles. Moreover, the Examiner provided "a basis in fact and/or technical reasoning to necessarily support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."

Applicant argues that Example 42 is drawn to a simple cationic liposome of undefined size, and not the composition of the claimed invention. It is noted that Example 42 was cited in the non-final Office action of 12/11/2007 in response to

Applicant's argument that the whole disclosure of Unger et al. is directed to contrast agents for imaging. Specifically, Example 42 clearly discloses that intracellular delivery of therapeutic agents is part of the invention of Unger et al. And even if Unger et al. would not have contemplated intracellular delivery, the claims are drawn to a composition and not to a method of delivery; there is nothing in the claims to differentiate the claimed composition from the composition taught by Unger et al.

In conclusion, Unger et al. as a whole anticipate the claimed invention. Unger et al. anticipate the claimed invention because they disclose 30 nm particles comprising a core provided by monomolecular layers of surfactant micelles (such as cetyl alcohol, i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent (such as a polynucleic acid) which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding protein shell, wherein the protein shell is covalently coupled with targeting ligands via Schiff linkages which are reduced by using lithium aluminum hydride (column 6, lines 52-61; column 8, lines 1-3 and 44-47; column 9, lines 36-50; column 10, lines 13-23; column 14, lines 10-12; column 15, lines 62-65; column 16, lines 18-26; column 17, line 60; column 18, line 61; column 28, lines 51-53; column 30, lines 18-32 , 66, and 67; column 31, lines 29 and 30; column 34, lines 24-49; column 38, lines 13-17; column 48, lines 43-45; column 49, lines 1-8; column 59, lines 66 and 67; column 60, lines 1-4 and 16-24). The limitation of the protein shell being precipitated by the cation wherein the cation is Li^+ is inherent to the nanocapsules of Unger et al., since the covalent attachment of the targeting ligand requires addition of lithium aluminum hydride, which would necessarily result in a precipitated protein shell

because Li^+ is a protein precipitating agent (see Kondo et al., Abstract). Therefore, Unger et al. disclose a specific embodiment, in full detail, which satisfies all the limitations of the claimed invention. The argument that this embodiment must be presented in the order of the claimed invention is not found persuasive because there is no requirement for such.

For these reasons Applicant's arguments are not found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 66, 67, 87, 88-94, 133-135, and 137-141 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. taken with Kondo et al., in view of Schneider et al. (FEBS Letters, 1998, 429: 269-273) for the reasons of record set forth in the non-final Office action of 12/11/2007. Applicant's arguments filed 07/30/2008 have been fully considered but they are not persuasive.

The teachings of Unger et al. anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139. Briefly, Unger et al. teach nanocapsules comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl

alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding lithium-precipitated protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137), that the nanocapsules have a size of about 30 nm (claims 66 and 139), that the nanocapsules can comprise a combination of two or more surfactants (claim 91), that the nanocapsules further comprise a biocompatible oil, such as peanut oil (claim 92) and a water-miscible solvent (claim 93). Kondo et al. provide evidence that the presence of Li^+ in the composition of Unger et al. necessarily results in a precipitated protein shell.

However, Unger et al. do not teach tenascin (claims 133, 134, 140, and 141) or a critical micelle concentration of about 200 micromolar (claim 89). Schneider et al. teach identification of a polypeptide derived from the C-terminus of tenascin (claims 133 and 140) capable to bind to $\alpha_9\beta_1$ integrins on the cell surface, i.e., Schneider et al. also teach a ligand that targets a receptor for tenascin (claims 143 and 141) (Abstract, p. 272, column 2 first paragraph and Fig. 4). Schneider et al. also teach their peptide as being suitable to mediate specific gene delivery to $\alpha_9\beta_1$ integrin-expressing cells (Abstract, p. 269, column 2, second paragraph, p. 272, column 2, second and third paragraphs). It

would have been obvious to one of skill in the art, at the time the invention was made to modify the nanocapsules of Unger et al. by replacing their targeting ligands with the peptide of Schneider et al. with the intent to target the particles to $\alpha_9\beta_1$ integrin-expressing cells, with a reasonable expectation of success. The motivation to do so is provided by Schneider et al., who teach that targeting $\alpha_9\beta_1$ integrin is promising for the development of gene therapy delivery vehicles since $\alpha_9\beta_1$ integrin is highly expressed on human airway epithelia irrespective of any clinical status (p. 269, column 1 bridging column 2). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in making such particles because Unger et al. teach that peptide ligands can be successfully included in their nanocapsules. With respect to the limitation of the surfactant having a critical micelle concentration of about 200 μm (claim 89), absent evidence of unexpected results, it would have been obvious to one of skill in the art to vary the parameters in a given method with the purpose of optimizing the results, i.e., to use a surfactant with the desired critical micelle concentration according to the intended use of the particles. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

With respect to Unger et al., Applicant's arguments are the same as above.

Additionally, Applicant argues that the teaching or suggestion to make the claimed combination must be found outside of the applicant's disclosure. Applicant submits that the only basis upon which one skilled in the art could construct the invention of claims 66 and 138 upon reading of Unger et al, would be with the critical knowledge of the Applicant's disclosed invention. Applicant also submits that the Examiner has failed to objectively determine whether the skilled artisan's expectation of success is great enough to render a resulting invention obvious. Applicant argues that the claimed invention would not have been obvious, nor would it have been assigned a probability of success that would have rendered it obvious, at the time it was made. Applicant argues that, at the time the claimed invention was made, the art viewed endocytosis as an attractive mechanism for targeted drug delivery into the cell. However, with respect to gene delivery for example, while this "seemingly simple concept has been pursued for more than a decade...in practice, this idea has been more difficult to implement effectively than perhaps had been originally anticipated .... Effective gene delivery by [the] receptor mediated mechanism requires specific vector binding, internalization, subcellular trafficking, endosomal escape, and unpackaging of the foreign DNA for desired gene expression. While this process offers a noninvasive mechanism to obtain selective intracellular localization of vectors, it may lead to destruction of delivered genes through intracellular pathways" with lysosomal degradation being particularly problematic (Varga et al., Biotech. Bioeng., 2000, 70: 593-605). With respect to caveolae, "there is to date little quantitative evidence showing caveolae to fulfill a role in mediating the uptake of DNA based therapeutics"

(Gumbleton et al., Pharm. Res., 17: 1035-1048). In view of these teachings, Applicant argues, one of skill in the art would not have viewed that the cumulative benefits of the present invention (i.e., lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery) as having a reasonable chance for being achieved. In light of the above discussion, Applicant submits that the Examiner has not established with a preponderance of evidence that Unger (with Kondo and Schneider) directs one of ordinary skill in the art to the claimed invention, nor has the Examiner established that the skilled artisan's expectation of success would have been great enough to render the claimed invention obvious at the time it was made.

Applicant also argues that Kondo et al. and Schneider et al. do not provide what Unger et al. lack. Applicant argues that she provided much evidence supporting that the intended purpose of the Unger et al. particles is ultrasound applications or therapeutic applications in conjunction with ultrasound. Applicant notes that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". In re Hedges, 783 F.2d 1038, 54 USLW 2455, 228 USPQ 685 (Fed. Circ. 1986), citing In re Wesslau, 353 F.2d 238,241,147 USPQ 391,393 (CCPA 1965). Applicant argues that legally, an invention is not obvious if the inventor would have been motivated 'to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible

choices is likely to be successful.' Likewise, Applicant argues, an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' In re PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1364 (Fed Cir. 2007), quoting In re O'Farrell, see also In re Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1166-67 (Fed.Cir.2006). Applicant submits that, in the instant case, all that has been provided by the combination of the references is simply an innumerable number of choices, as to which of the possible choices are likely to be successful, in that in particular, Unger et al. teaches that sizes of 200 nm and above are preferred. Applicant argues that the Examiner has failed to sufficiently explain, with a preponderance of evidence and in a manner grounded by case law, why one of ordinary skill in the art would make the designated selections from the vast disclosure of Unger et al, in an attempt to form a composition comprising an ultra small particle comprising elements of the instant claims, particularly with respect to claims 133, 134, 140, 141 or claim 89. Applicant also points out that the Examiner has failed to articulate why the skilled artisan's expectation of success would have been great enough to render the claimed invention, as a whole, obvious at the time it was made. The ultra small particles for therapeutic agent delivery as taught by Applicant provide the simultaneous benefits of lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery, in which would not have been predictable at the time the present invention was made. Accordingly, since these benefits were not predictable at the time the invention

was made, these benefits were unappreciated by the Unger et al., Schneider, and Kondo references and thus there is no teaching, suggestion or prediction that such particles would be successful, particularly with respect to claims 133, 134, 140, 141 or claim 89. Therefore, Applicant requests reconsideration of the rejection.

Applicant' arguments are acknowledged however, the rejection is maintained for the following reasons:

With respect to Unger et al., see above. Applicant argues that the claimed particles provide cumulative benefits such as lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery. With respect to this argument, it is noted that such limitations are not recited in the claims; even if they were in the claims, the claims are drawn to a composition and not to a method of delivery which avoids lysosomal degradation, or which provides cargo protection, uniform gene expression, and cell specific delivery; reciting such would be an intended use which would not state any distinct definition of any of the claimed limitations such as to differentiate the claimed composition from the composition taught by the prior art and therefore, would not impart patentability to composition claims. There is nothing in the instant claims to make the claimed composition distinct from the composition of Unger et al. Therefore, the argument that one of skill in the art would not have been expected to have a reasonable expectation of success in achieving the claimed invention is not found persuasive. Unger et al. do anticipate the claimed particles and therefore, therefore, the instant invention was achieved before the instant application was filed (i.e., the invention was also achieved without a knowledge of the Applicant's disclosure). Unger et al.

anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139, but not claims 89, 133, 134, 140, 141, and 143. Therefore, the secondary references have nothing to remedy in claims 66, 67, 87, 88, 90-94, 135, and 137-139. Claim 89 recites that the surfactant has a critical micelle concentration of about 200 μm; it would have been obvious to the ordinary skilled artisan to vary the parameters with the purpose of optimizing the results, i.e., to use a surfactant with the desired critical micelle concentration according to the intended use of the particles. Claims 133, 134, 140, and 141 are drawn to using tenascin as a targeting ligand. Schneider et al. teach using tenascin polypeptides to mediate specific gene delivery to $\alpha_9\beta_1$ integrin-expressing cells. It is noted that, although they do teach targeting ligands, Unger et al. do not specifically teach tenascin polypeptides. However, being aware of the art as a whole (for example the teachings of Schneider et al.), it would have been obvious to one of skill in the art to use such polypeptides to achieve the predictable result of delivering therapeutics to $\alpha_9\beta_1$ integrin-expressing cells. For these reasons, it is concluded that the claimed limitations (i.e., using tenascin polypeptides as targeting ligands and a detergent with a CMC of less that 200 μM) were *prima facie* obvious at the time the invention was made and therefore, the rejection is maintained.

12. Claims 66, 67, 87, 88, 90-94, and 135-139 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. taken with Kondo et al., in view of each Medina (U.S. Patent No. 5,650,543), Quay (U.S. patent No. 5,707,606), and Duquemin et al. (J Pharm Pharmacol, 1985, 37: 698-702, Abstract).

The teachings of Unger et al. anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139. Briefly, Unger et al. teach nanocapsules comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding lithium-precipitated protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137), that the nanocapsules have a size of about 30 nm (claims 66 and 139), that the nanocapsules can comprise a combination of two or more surfactants (claim 91), that the nanocapsules further comprise a biocompatible oil, such as peanut oil (claim 92) and a water-miscible solvent (claim 93). Kondo et al. provide evidence that the presence of Li^+ in the composition of Unger et al. necessarily results in a precipitated protein shell.

Unger et al. do not teach acetylenic diols (claim 136). Medina teaches the acetylenic diol 2,4,7,9-tetramethyl-5-decyne-4,7-diol (i.e., the species recited in claim 136) and its ethoxylates as excellent surfactants because of their ability to decrease the surface tension (Abstract, column 1, lines 30-35, column 3, lines 3-5). Medina does not teach using their 2,4,7,9-tetramethyl-5-decyne-4,7-diol for the fabrication of

nanoparticles. However, Quay teaches the use of acetylenic diols or blends thereof for the preparation of stable and biocompatible colloidal dispersions used for enhancing the contrast in an ultrasound image (Summary of the invention, column 3, lines 15-19, column 7, lines 9-16). Based on the teachings of Quay one of skill in the art would have known that acetylenic diols could be used to obtain biocompatible particles suitable for the delivery of bioactive agents. Based on the teachings of Medina (i.e., the ability to decrease the surface tension), one of skill in the art would have known that the use of acetylenic diols such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol would result in small particles that are more efficient in delivering bioactive components. It is noted that one of skill in the art would have known that reducing the surface tension would result in smaller particles because the prior art teaches this (see for example Duquemin et al., Abstract). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the particles of Unger et al. by using 2,4,7,9-tetramethyl-5-decyne-4,7-diol, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Medina clearly teaches that 2,4,7,9-tetramethyl-5-decyne-4,7-diol is able to decrease the surface tension. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that acetylenic diols can be successfully used in the preparation of particles for the *in vivo* delivery of agents. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments regarding Unger et al., are the same as above. In addition, Applicant argues that the secondary references do not provide what is lacking in Unger et al.

The reply to these arguments is the same as above. Unger et al. anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139, but not claim 136. Therefore, the secondary references have nothing to remedy in claims 66, 67, 87, 88, 90-94, 135, and 137-139. Claim 136, the only claim not anticipated by Unger et al., recites a particular species of surfactant (i.e., 2,4,7,9-tetramethyl-5-decyne-4,7-diol). This surfactant species was known in the prior art and one of skill in the art would have been motivated to use it for the reasons set forth in the non-final Office action of 12/11/2007. It is concluded that the claimed limitation (i.e., using 2,4,7,9-tetramethyl-5-decyne-4,7-diol) was *prima facie* obvious at the time the invention was made and therefore, the rejection is maintained.

New rejections

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ

619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 11 of copending Application No. 12/027,863. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that the instant rejection has not been previously presented because Application No. 12/027,863 was filed on 02/07/2008, which is after the mailing date of the non-final Office action of 12/11/2007. It is also noted that Application No. 12/027,863 is a continuation of Application No. 10/958,999 and that claims 8 and 11 of Application No. 12/027,863 are identical to claims 10 and 13 of the abandoned Application No. 10/958,999. Therefore, the instant rejection is the same as the obviousness-type double patenting rejection previously made over claims 10 and 13 of Application No. 10/958,999 (see the non-final Office action of 12/11/2007).

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139), which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136. The specification defines that the polynucleotide could be an anti-sense DNA (p. 23, line 1).

The application claims recite a collection of particles comprising an agent, a surfactant molecule having an HLB of less than 6.0, a polymer soluble in aqueous solution, wherein the collection of particles has an average diameter of less than about 100 nm as measured by atomic force microscopy after drying and wherein the agent is an anti-sense nucleic acid (claim 8). The collection of particles further comprises a cell recognition agent (claim 11). The specification defines that the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol, as recited in the instant claims 87, 88, 90, and 136 (i.e., a surfactant with an HLB of less that 5.0), the particles further

comprise Li^+, wherein Li^+ is used to precipitate the biocompatible polymer that surrounds the micelles comprising the surfactant and bioactive agent, and the polymer can be tenascin (p. 8, lines 8 and 9, p. 12, lines 8-23, p. 17-18, Table 1, p. 56, lines 5 and 6). With respect to the limitation of nanocapsule, the specification defines that the particles can be formulated as nanocapsules (p. 13, lines 8 and 9). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, one of skill in the art would know to do this because the art teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims and the instant claims are obvious variants of one another.

Conclusion

15. The filing of Application No. 12/027,863 after the mailing date of the non-final Office action necessitated the new ground of obviousness-type double patenting rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/
Examiner, Art Unit 1633